REMARKS

Claim 1 is currently pending in the above-identified patent application and remaining for consideration, claims 22-50 having been cancelled by this amendment.

Claim 1 was rejected under the second paragraph of 35 U.S.C. § 112 as allegedly vague and indefinite.

Claim 1 was rejected under the first paragraph of 35 U.S.C. § 112 as failing to comply with the written description requirement.

Claim 1 was rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,242,568 to Barbas et al. ("Barbas '568").

Examination has been limited to SEQ ID NO:41 as indicated.

Reexamination of the application as amended, reconsideration of the rejections, and allowance of claim 1 are respectfully requested.

The three-month shortened statutory period for response expires on September 12, 2007. Accordingly, this response is being filed in a timely manner.

I. AMENDMENTS TO THE APPLICATION

Entry of the amendments to the claims is respectfully requested. As detailed below, these amendments introduce no new matter.

The amendment to claim 1 is supported by Figure 1 of the above-identified patent application. This figure lists the binding specificity of each of the zinc finger nucleotide binding domains referenced in the application by their SEQ ID NOs. This amendment corrects a minor typographical error in previously submitted claim 1 and does not present new matter.

II. THE REJECTION UNDER THE SECOND PARAGRAPH OF 35 U.S.C. § 112

Claim 1 was rejected under the second paragraph of 35 U.S.C. § 112, allegedly for indefiniteness.

Specifically, the Examiner stated that it was not clear what was intended by the phrase " . . . such that the nucleotide binding activity of the polypeptide resides in the nucleotide binding region having the sequence SEQ ID NO: 41 . . .". The Examiner stated that this phrase could be interpreted in two ways. The first interpretation of this phrase is that only the nucleotide binding regions having SEQ ID NO: 41 bind to the nucleotide molecule. The second interpretation of this phrase is that SEQ ID NO: 41 can be one of several nucleotide binding regions that bind to the nucleotide molecule, and the activity is transcription resulting from the collective binding of the nucleotide binding regions (in which at least one must be SEQ ID NO: 41).

The Examiner stated that the interpretation of this phrase needs to be clarified.

The second interpretation of this phrase is correct. At page 6, line 28, to page 7, line 4, the specification makes it clear that polypeptides according to the present invention can include multiple zinc finger nucleotide binding domains, not all of which bind a GNN triplet. The specification states:

A zinc finger-nucleotide binding polypeptide refers to a polypeptide which is a derivatized form of a wild-type zinc finger protein or one produced through recombination. A polypeptide may be a hybrid which contains zinc finger domain(s) from one protein linked to zinc finger domain(s) of a second protein, for example. The domains may be wild type or mutagenized. A polypeptide includes a truncated form of a wild type zinc finger protein. Examples of zinc finger proteins from which a polypeptide can be produced include TFIIIA and zif268.

This discussion makes it clear that polypeptides according to the present invention can include multiple zinc finger nucleotide binding domains, not all of which bind a GNN triplet. This interpretation is also completely in accord with the use of zinc fingers according to the present invention as gene switches.

Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. THE REJECTION UNDER THE FIRST PARAGRAPH OF 35 U.S.C. § 112 FOR LACK OF COMPLIANCE WITH THE WRITTEN DESCRIPTION REQUIREMENT

Claim 1 was rejected under the first paragraph of 35 U.S.C. § 112 as failing to comply with the written description requirement.

Specifically, the Examiner stated that claim 1 had been amended to state that SEQ ID NO: 1 binds to GAC, GTC, GCT, and GCC. In Figure 1 of the drawings of the above-identified patent application, SEQ ID NO: 41 was shown to bind to nucleotide sequences GAG, GTG, GCT, and GCC. The inclusion of GAC and GTC was stated to be new matter.

This rejection is obviated by the amendment of claim 1 to recite the correct nucleotide sequences, namely GAG, GTG, GCT, and GCC. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. THE REJECTION UNDER 35 U.S.C. § 102(e)

Claim 1, directed to SEQ ID NO: 41, was rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,242,568 to Barbas et al. ("Barbas et al. '568"). This rejection is respectfully traversed.

It was stated that Barbas et al. '568 taught a C7 zinc finger nucleotide binding polypeptide containing SEQ ID NO: 41 (KSADLKR) in Figure 15 and in SEQ ID NO: 42 of Barbas et al. '568 at residues 20-26.

This rejection is being maintained because the Examiner has been interpreting the phrase "such that the nucleotide binding activity of the polypeptide resides in the nucleotide binding region having the sequence SEQ ID NO: 41 . . ." in terms of the second interpretation, i.e., that it was intended that the binding of SEQ ID NO: 41 to the nucleotide molecule be one of several nucleotide binding regions that bind to the molecule. The activity of the polypeptide was stated to be transcription resulting from the collective binding of the nucleotide binding regions (in which at least one is SEQ ID NO: 41 of the present application).

Although, as explained above, this interpretation of this phrase is correct, Barbas et al. '568 still does not anticipate claim 1 of the present application, and this rejection is respectfully traversed.

This rejection is respectfully traversed because the teachings of Barbas et al. '568 do not establish that "the nucleotide-binding activity of the polypeptide resides in the nucleotide-binding region having the sequence of SEQ ID NO:41" as required by pending

claim 1. This interpretation requires, at a minimum, that SEQ ID NO: 41 contribute to the nucleotide binding activity of the polypeptide, even though other zinc finger nucleotide binding domains also can contribute to the total nucleotide binding of the polypeptide. This interpretation does not encompass polypeptides or chimeric proteins in which SEQ ID NO: 41 fails to contribute to the total nucleotide binding of the polypeptide or chimeric protein.

The C7 zinc finger nucleotide binding polypeptide of Figure 15 of Barbas et al. '568 (SEQ ID NO: 42 of Barbas et al. '568) seemingly has three repeats of the motif Lys-Ser-Ala-Asp-Leu-Lys-Arg (KSADLKR) at amino acids 20-26, 50-56, and 80-86.

However, at column 29 of the specification of Barbas '568, it states that the C7 finger can be constructed according to the scheme:
MKLLEPYACPVESCDRRFSKSADLKRHIRHTGEKP-
(YACPVESCDRRFSKSADLKHIRIHTGEKP)$_{1-11}$, (SEQ ID NO: 39) where the sequence of the last linker is subject to change since it is at the terminus and not involved in linking two fingers together (column 29, lines 56-64 of Barbas '568). In this scheme, the third repeat of the motif Lys-Ser-Ala-Asp-Leu-Lys-Arg (KSADLKR) is not exact and is in fact Lys-Ser-Ala-Asp-Leu-Lys-His (KSADLKH), as shown directly in SEQ ID NO: 39. It is this protein, with the imperfect third repeat, that is described as binding the designed target sequence GCG-GCG-GCG (SEQ ID NO: 32 of Barbas et al. '568) in an oligonucleotide hairpin with an affinity of 9 nM, as compared to an affinity of 300 nM for an oligonucleotide encoding the GCG-TGG-GCG sequence (Barbas et al. '568, column 29, line 64 to column 30, line 3; see also Example 13, describing the construction of this zinc finger nucleotide binding polypeptide).

In regard to the Examiner's questions, Example 13 clearly shows the binding of GCG by SEQ ID NO: 41 of the present application (i.e., KSADLKR). The relevant portion of this example, at column 49, line 18 to column 50, line 5, reads as follows:

Following mutagenesis and selection of variants of the Zif268 protein in which the finger 1 specificity or affinity was modified (See EXAMPLE 7), proteins carrying multiple copies of the finger may be constructed using the TGEKP linker sequence by methods known in the art. For example, the C7 finger may be constructed according to the scheme:

MKLLEPYACPVESCDRRFSKSADLKRHIRHTGEKP-

(YACPVESCDRRFSKSADLKHIRIHTGEKP)$_{1-11}$, where the sequence of the last linker is subject to change since it is at the terminus and not involved in linking two fingers together. An example of a three finger C7 construction is shown in FIG. 15. This protein binds the designed target sequence GCG-GCG-GCG (SEQ ID NO: 32) in the oligonucleotide hairpin CCT-CGC-CGC-CGC-GGG-TTT-TCC-CGC-GCC-CCC GAG G with an affinity of 9 nM, as compared to an affinity of 300 nM for an oligonucleotide encoding the GCG-TGG-GCG sequence (as determined by surface plasmon resonance studies). Proteins containing 2 to 12 copies of the C7 finger have been constructed and shown to have specificity for their predicted targets as determined by ELISA (see for example, Example 7). Fingers utilized need not be identical and may be mixed and matched to produce proteins which recognize a desired target sequence.

This Example clearly establishes that the repeated sequence KSADLKR binds the repeated motif GCG in the oligonucleotide, given the colinearity of the binding between the amino acid sequences of the zinc finger nucleotide binding protein and the

Moreover, claim 1, as amended, recites that the zinc finger nucleotide binding region binds a nucleotide sequence selected from the group consisting of GAG, GTG, GCT, and GCC. None of these nucleotide sequences is bound by the protein recited in Barbas '568, whose binding specificity is defined above, according to the results in Barbas '568 itself (i.e,

Example 13, as quoted above). There is no other teaching or suggestion that this protein can specifically bind any of GAG, GTG, GCT, or GCC.

The results of Barbas '568 suggest that the Lys-Ser-Ala-Asp-Leu-Lys-Arg (KSADLKR) motif and the inexact repeat of that motif, Lys-Ser-Ala-Asp-Leu-Lys-His (KSADLKH), found in the protein described in Barbas '568, bind the triplet GCG. This is because it is known that when a zinc finger nucleotide binding protein binds a nucleic acid sequence, the amino-terminus of that zinc finger nucleotide binding protein binds to the 3'-end of the nucleic acid sequence and the carboxyl-terminus of that zinc finger nucleotide binding protein binds to the 5'-end of the nucleic acid sequence. This pattern is independent of the particular nucleotides and amino acids involved in the binding; the polarity of the binding is invariant, at least for all known zinc finger nucleotide-binding proteins of the general structure of the zinc finger nucleotide-binding protein of the present invention.

Therefore, according to the results of Barbas '568, the sequences KSADLKR or KSADLKH bind to the triplet GCG, and not to TGG. These results follow from the placement of these motifs in the zinc finger protein described in Barbas '568.

The less-specific binding results seen when the middle triplet is changed from GCG to TGG indicates the sensitivity of the binding to the three-dimensional structure of the nucleotide. It also indicates that the binding can be greatly affected even when the triplets that bind the zinc finger nucleotide binding domains that are amino- or carboxyl-terminal to the mismatched domain should still be bound. Therefore, it is necessary to take into account the entire three-dimensional structure of a zinc finger nucleotide-binding polypeptide to determine its binding specificity for a particular nucleotide sequence. This is in accord with the interpretation of the phrase "such that the nucleotide binding activity of the polypeptide resides in the nucleotide binding region having the sequence SEQ ID NO: 41 . . ." in terms of the second possible proposed interpretation, i.e., that it was intended that the binding of SEQ ID NO: 41 to the nucleotide molecule be one of several nucleotide binding regions that bind

to the molecule. Notwithstanding this interpretation of this phrase, Barbas '568 fails to disclose a zinc finger nucleotide binding polypeptide of appropriate specificity.

As emphasized below, this shows that the zinc finger nucleotide-binding polypeptide of Barbas '568 and the zinc finger nucleotide-binding polypeptide of claim 1 of the present invention are different molecules.

Accordingly, because of the different binding specificity for KSADLKR in the zinc finger protein described in Barbas '568, there is no disclosure in Barbas '568 of a zinc finger binding protein "that consists essentially of a nucleotide binding region having the sequence of SEQ ID NO:41 such that the nucleotide-binding activity of the polypeptide resides in the nucleotide-binding region having the sequence of SEQ ID NO:41 and wherein the nucleotide-binding region having the sequence of SEQ ID NO: 41 binds a nucleotide sequence selected from the group consisting of GAG, GTG, GCT, and GCC" as required by claim 1 as amended herein.

A rejection under 35 U.S.C. §102 requires that the claimed subject matter be described in its entirety in a single reference. Kalman v. Kimberly-Clark Corp., 218 U.S.P.Q. 781, 789 (Fed. Cir. 1983), cert. denied, 465 U.S. 1026 (1984). In re Marshall, 198 U.S.P.Q. 344 (C.C.P.A. 1978). Missing elements cannot be supplied by the knowledge of one skilled in the art or by the disclosure of another reference. Structural Rubber Products Co. v. Park Rubber Co., 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984).

Moreover, the properties and activity of a compound, such as the zinc finger binding polypeptide of claim 1, must be considered as an inseparable part of the compound for the consideration of patentability. In re Papesch, 137 U.S.P.Q. 43 (C.C.P.A. 1963). These properties and activity encompass the nucleotide binding activity of these zinc finger polypeptides. This means that the lack of specific binding of any of the triplets GAG, GTG, GCT, and GCC by the zinc finger nucleotide binding polypeptide described in Barbas '568 precludes any anticipation of claim 1 by Barbas '568. The different activity indicates that the

proteins are not the same, notwithstanding the interpretation of the phrase "such that the nucleotide binding activity of the polypeptide resides in the nucleotide binding region having the sequence SEQ ID NO: 41 . . ." proposed by the Examiner.

The transitional phrase "consisting essentially of" or equivalent language limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristics of the claimed invention." In re Herz, 190 U.S.P.Q. 461, 463 (C.C.P.A. 1976). The transitional phrase "consisting essentially of" is not equivalent to "comprising." Claims using the transitional phrase "consisting essentially of" are properly considered to be partially open rather than open. In re Garnero, 162 U.S.P.Q. 221, 223 (C.C.P.A. 1969). Interpreting this transitional phrase as open is not consistent with the case law.

The existence of other nucleotide binding regions in the polypeptide of Figure 15 of Barbas '568 does affect the "basic and novel characteristics" of the claimed invention, as the activity of these polypeptides resides in their specific binding of nucleotide sequences. This is clear from the discussion of Example 13 of Barbas '568.

The foregoing discussion establishes that the secondary and tertiary structure of the protein domains that make up the zinc finger nucleotide binding domains is of critical importance in determining the specificity and affinity of binding of a nucleotide of a defined sequence. This means that any change in the secondary or tertiary structure of the polypeptide can affect the binding of a nucleotide of a defined sequence. It is a well-established principle of protein chemistry that the secondary and tertiary structure of a polypeptide is determined by its primary structure, i.e., the linear sequence of amino acids that constitutes the polypeptide. Therefore, a change in the specificity or affinity of the binding of a nucleotide of a defined sequence by a polypeptide reflects a change in the secondary or tertiary structure of the polypeptide and thus a change in the primary structure of the polypeptide. Such a change must affect the "basic and novel characteristics" of the protein, by the very definition of a protein and its activity.

This is emphasized by the difference in binding specificity between the polypeptide of Barbas '568 and the polypeptide of claim 1 of the pending application. This different binding specificity indicates that the "basic and novel characteristics" of the polypeptides are different, as the binding specificity for nucleotide sequences is the entire function of these zinc finger polypeptides. Thus, the polypeptide of Barbas '568 cannot anticipate claim 1 of the pending application.

The use of the transitional phrase "consisting essentially of", therefore, precludes the possibility of a rejection under 35 U.S.C. § 102(e) over Barbas '568. The rejection over Figure 15 of Barbas '568 is over a polypeptide that contains a framework that affects the ability of the protein to bind the required nucleotide sequences. It is a well-understood principle of protein structure that the secondary and tertiary structure of a protein is directly specified by the primary structure of the protein. The ability of an amino acid sequence to act as a zinc finger motif and bind a specified triplet is therefore highly dependent on the secondary and tertiary structure of the protein. The zinc finger proteins of Barbas '568, including that of Figure 15, are provided by minimal modification of the wild-type zinc finger proteins Zif268.

In contrast, the zinc finger polypeptides of the present invention are derived by modular assembly and are not directly related to Zif268 in their primary sequence. This means that the secondary and tertiary structures of the proteins differ significantly. This difference in secondary and tertiary structures undoubtedly is the reason for the difference in binding specificity between the zinc finger polypeptides of claim 1 of the present invention and the zinc finger polypeptides described in Barbas '568.

The application of this principle of protein chemistry meets the burden of showing that the introduction of additional components would materially change the characteristics of applicant's invention. In re De Lajarte, 143 U.S.P.Q. 256 (C.C.P.A. 1964). Where the omission of ingredients present in the prior art composition results in a

composition having basic or novel characteristics not possessed by the prior art, use of the transitional phrase "consisting essentially of" in the claims to exclude the omitted ingredients avoids anticipation. Id.

The "basic or novel characteristics" of the present application are not present in Barbas '568, based on the actual difference in binding specificity as shown, for example, in Example 13 of Barbas '568. This is a material change in characteristics, because the most significant property of such zinc finger polypeptides is their ability to bind a specific nucleic acid sequence, such as a triplet.

Additionally, Barbas '568 cannot anticipate claim 1 by inherency. Inherency cannot be established by mere possibilities or probabilities. The law regarding anticipation by inherency is well settled. One clear requirement of finding anticipation under the doctrine of inherency is that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 U.S.P.Q. 2d 1955, 1957 (Fed. Cir. 1993); In re Oelrich, 666 F.2d 578, 581-82, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) ("To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'").

Therefore, the absence of any basis in Barbas '568 from which it can be concluded with certainty that SEQ ID NO: 41 of the present invention binds a nucleotide of the appropriate sequence negates any possibility that Barbas '568 anticipates claim 1 of the present application by inherency.

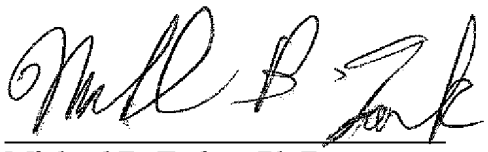
Accordingly, the Examiner is respectfully requested to withdraw this rejection and allow claim 1.

V. CONCLUSION

In conclusion, claim 1 is patentable over the prior art of record, whether considered individually or in combination. Accordingly, prompt allowance of this claim is respectfully requested. This claim particularly points out and distinctly claims what Applicant regards as his invention, and meets the written description requirement of the first paragraph of 35 U.S.C. § 112.

If any issues remain, the Examiner is respectfully requested to telephone the undersigned at (858) 200-0581.

Respectfully submitted,



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